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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/626,943	07/25/2003	Joseph T. Rubino	AM-100802	3231

38199 7590 04/04/2007

HOWSON AND HOWSON
CATHY A. KODROFF
SUITE 210
501 OFFICE CENTER DRIVE
FT WASHINGTON, PA 19034

EXAMINER	
POLANSKY, GREGG	
ART UNIT	PAPER NUMBER
1609	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/04/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/626,943	RUBINO ET AL.	
	Examiner	Art Unit	
	Gregg Polansky	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *1-11 and 22-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Applicant's election of Group II in the reply filed on 10/11/2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Group II, as defined in the Requirement for Election/Restriction filled on 9/21/2006, comprises Claims 12-21. Applicant's reply to the Restriction Requirement included Claim 22 in the elected group. Examination will proceed on Group II as defined in the 9/21/2006 office action; that is, Claims 12-21. This restriction requirement is **Made Final**.

3. Applicant elected species are from Examples 2 and 8 in the Specifications

4. Claim(s) 1-30 are pending.

5. Claim(s) 1-11 and 22-30 are withdrawn from consideration whereas they are contained in non-elected groups.

Specification Objections

6. The abstract of the disclosure is objected to because it is not descriptive enough of the elected invention. The abstract should be between 50 and 150 words in length and should provide a description of the elected invention; i.e., the instant abstract should specify that the parenteral formulation comprising CCI-779 also comprises an alcoholic solvent, an antioxidant, a diluent solvent, and a surfactant. It is also useful to

mention the preferred embodiment in the abstract. Correction is required. See MPEP § 608.01(b).

7. The use of the following trademark has been noted in this application: CREMOPHOR. It should be written in all capital letters wherever it appears; or alternatively, it should be denoted with the registered trademark symbol, ®, and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks.

Claim Objections

8. Claims 17-21 objected to because of the following informalities: the current wording is awkward and either technically or grammatically incorrect. In light of the specification, the Examiner interprets these claims to be limiting the concentration of specific components of the instant formulation, however, the wording is awkward. The Applicant is advised to amend the claims as follows:

a. For claim 17, replace "CCI-779 comprises from about 2.5 mg/mL to about 10 mg/mL" with - - the formulation comprises a concentration of CCI-779 from about 1 mg/mL to about 25 mg/mL - -.

b. For claim 18, replace "CCI-779 comprises from about 2.5 mg/mL to about 10 mg/mL" with - - the formulation comprises a concentration of CCI-779 from about 2.5 mg/mL to about 10 mg/mL - -.

c. For claim 19, replace "antioxidant comprises from about 0.0005% to 0.5% w/v of the formulation" with - - formulation comprises a concentration of antioxidant from about 0.0005% to 0.5% w/v - -.

d. For claim 20, replace "surfactant comprises from about 0.5% to about 10% w/v of the formulation" with - - formulation comprises a concentration of surfactant from about 0.5% to about 10% w/v - -.

e. For claim 21, replace "solvent comprises from about 10% to about 90% w/v of the formulation" with - - formulation comprises a concentration of solvent from about 10% to about 90% w/v - -.

Appropriate correction is required.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 12, 13, and 15 rejected under 35 U.S.C. 102(e) and 35 U.S.C. 102(a) as being anticipated by US 2002/0013335 (Azrolan, et al.). Claim 12 is drawn to a

parenteral formulation comprising rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid (CCI-779), an alcoholic solvent, an antioxidant, a diluent solvent , and a surfactant. Claim 13 is drawn to the parenteral formulation of Claim 12 where the alcoholic solvent is ethanol or polypropylene (elected species). Claim 15 is drawn to the parenteral formulation of Claim 12 where the diluent solvent is ethanol or polyethylene glycol 400 (elected species).

11. Azrolan, et al. teaches that rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid (CCI-779) is a member of a group of compounds that are derivatives of the rapamycin nucleus (*see* Azrolan, et al., paragraph 14). Azrolan, et al. teaches the parenteral administration of CCI-779 and other rapamycins and suggests a solvent of water, ethanol, glycerol, propylene glycol and polyethylene glycol or a combination thereof, a surfactant, such as hydroxylpropylcellulose, a preservative (*see* Azrolan, et al., paragraphs 28 and 29) and antioxidant (*see* Azrolan, et al., Claim 14). Therefore, Azrolan, et al. teaches all of the elements of Claims 12, 13, and 15 of the instant application.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1,148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 12-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 2002/0013335 (Azrolan, et al.) in view of US 5516770 (Waranis, et al) and GB 2327611 (Haeberlin, et al.).

Descriptions of Claims 12, 13, and 15 are presented above. Claim 14 is drawn to the parenteral formulation of Claim 12 where the antioxidant is d,l-α-tocopherol or citric acid (elected species). Claim 16 is drawn to the parenteral formulation of Claim 12 where the surfactant is polysorbate 80 (elected species). Claims 17 and 18 are drawn to the formulation of Claim 12, wherein CCI-779 comprises from about 1 mg/ml to about

25 mg/ml and from about 2.5 mg/ml to about 10 mg/ml respectively. Claim 19 is drawn to the parenteral formulation of Claim 12 wherein the antioxidant comprises from about 0.0005% to about 0.05% w/v of the formulation. Claim 20 is drawn to the parenteral formulation of Claim 12 wherein the surfactant comprises from about 0.5% to about 10% w/v of the formulation. Claim 21 is drawn to the parenteral formulation of Claim 12 wherein the solvent comprises from about 10 % to about 90% w/v of the formulation.

16. The teachings of Azrolan, et al. are presented above. Additionally, Azrolan, et al teaches and incorporates by reference preferred parenteral formulations of rapamycins taught in US 5516770 (*see* Azrolan et al., paragraph 29).

Azrolan, et al., does not teach a specific antioxidant (e.g., citric acid or d,l-α-tocopherol) or the surfactant, polysorbate 80. Also, Azrolan, et al., does not teach the concentrations of CCI-779, antioxidant, surfactant, or solvent as specified in the claims of the instant application.

17. US 5516770 (Waranis, et al.) teaches an injectable rapamycin solution comprised of a mixture of a concentrate of rapamycin in propylene glycol with a diluent of polyethylene glycol 400 and a polyoxyethylene sorbitan ester (e.g., polysorbate 80) and water (*see* US 5516770, examples 1-3), yielding an injectable formulation concentration of rapamycin of 0.2 mg/ml to 4 mg/ml (*see* US 5516770, column 2, lines 44-47), with 0.07-9.5% polysorbate 80 and 12-87% glycols (*see* US 5516770, column 3, lines 29-54). These concentrations are within the concentration ranges specified in the claims of the instant application. US 5516770 does not teach use of an antioxidant. US 5516770 teaches formulations of rapamycins, but not CCI-779 specifically. However,

Azrolan, et al. teaches US 5516770 as a preferred parenteral formulation for CCI-779 (supra).

18. GB 2327611 (Haeberlin, et al.) teaches the use of various carboxylic acids to stabilize (i.e. preserve) oral and parenteral formulations of macrolides, preferably a rapamycin. The preferred acids include malonic acid, oxalic acid, citric acid, and lactic acid (*see* GB 2327611, page 4, lines 15-22). GB 2327611 teaches a 0.05% to 5% acid concentration range (which encompasses the instant invention citric acid concentration specification) and further discloses that the preferred amount of acid may be determined by routine experimentation. GB 2327611 gives as an example, a formulation of a rapamycin with ethanol, Cremophor® EL, and citric acid. They present other examples of rapamycin formulations which include the use of 1,2 propylene glycol as a solvent and d,l-α-tocopherol as an antioxidant.

19. It would have been obvious to one of ordinary skill in the art at the time of the invention to one who was motivated to produce a parenteral formulation of CCI-779, to combine the teachings of Azrolan, which teaches the essential elements of said formulation, with those of US 5516770, and GB 2327611 which teach individual elements of WO 0197809 in more detail. US 5516770 teaches the concentrations of the solvents (e.g. propylene glycol and polyethylene glycol 400), rapamycin, and a specific surfactant (polysorbate 80) for a parenteral rapamycin formulation. GB 2327611 teaches the use of acetic acid and d,l-α-tocopherol as a stabilizer in a rapamycin parenteral formulation. Azrolan, et al's teaching of including an antioxidant and preservative in rapamycin formulations would motivate one to combine Azrolan, et

al. with GB 2327611. One would be motivated to combine Azrolan and US 5516770, since Azrolan specifies and incorporates by reference the parenteral formulations of US 5516770. One would have been motivated to perfect a parental formulation of CCI-779 to reduce the bioavailability uncertainties of other forms of administration (e.g. oral), leading to more accurate and reproducible doses of the agent.

Conclusion

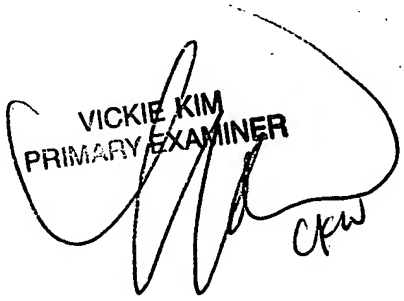
20. Claims 12-21 are rejected.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregg Polansky whose telephone number is (571) 272-9070. The examiner can normally be reached on M-F 7:30 A.M. - 5:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisors, Cecilia Tsang or Janet Andres can be reached on (571) 272-0562 or (571) 272-0867 respectively. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Gregg Polansky



Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :10/21/03, 11/21/03, 10/11/06, 02/26/07.